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Lactobacillus delbrueckii as the Cause of Urinary Tract Infection▽

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Lactobacilli are part of the normal bacterial flora of the vagina and are typically considered contaminants when cultured from urine specimens of female patients. Here we describe the case of a female patient with chronic pyuria and urinary tract symptoms in which *Lactobacillus delbrueckii* was determined to be the causative microorganism.

CASE REPORT

An 85-year-old female with recurrent urinary tract infections called her gynecologist reporting painful urination, frequency, and urgency. A prescription for ciprofloxacin at 250 mg twice a day (BID) for 7 days (adjusted for a decreased glomerular filtration rate) was called in to her local pharmacy. She experienced no relief of symptoms with this treatment.

Two weeks later, she was seen in the clinic. She denied fevers or flank pain but continued to have urgency, dysuria, and a frequency of every 1.5 h, including nocturia. Her further pertinent medical and surgical history included a stage III cystocele, vaginal prolapse repair in 1999, total abdominal hysterectomy with bilateral salpingoopherectomy in 1962, hypothyroidism, and two prior discectomies. She intermittently applied vaginal estradiol. She had not used pessaries for her vaginal prolapse in 9 years and had no recent indwelling Foley catheter or intermittent self-catheterization. Examination revealed inflamed labia minora. The postvoiding residual was 100 ml. A straight catheter sample was obtained for culture and due to well-documented allergies to penicillin, sulfa, and nitrofurantoin, another course of ciprofloxacin was prescribed (250 mg BID for 10 days). Nystatin-triamcinolone ointment and zinc oxide were prescribed for the perivulvar dermatitis. Urine culture yielded >50,000 CFU/ml of a microaerophilic, alpha-hemolytic, gram-positive bacillus that was both catalase and oxidase negative. In view of these characteristics together with a very characteristic Gram stain morphology, the organism was presumptively identified as a *Lactobacillus* species and was judged to be a contaminant.

The nocturia, frequency, and dysuria did not resolve, and she returned 6 weeks later. She described a postvoiding sensation of "sand in my bladder." No systemic symptoms occurred in the interval. An examination showed improved but residual erythema and mild edema of the labia minora and introitus. The vaginal epithelium was intact with mild erythema suggesting atrophy. A straight catheter urine sample was obtained, and the patient was given another course of ciprofloxacin for 10 days. Urine microscopy showed significant pyuria with white blood cell (WBC) clumps and many bacteria, and culture again yielded >50,000 CFU/ml of a *Lactobacillus* sp., which was again considered to be a contaminant.

After no improvement following the third course of ciprofloxacin treatment, an infectious disease consult was obtained. Urine studies were repeated. Again, urine microscopy showed significant pyuria, WBC clumping, and many bacteria, and culture grew >50,000 CFU/ml of a *Lactobacillus* species. Etest MICs determined on Mueller-Hinton agar incubated anaerobically were as follows: doxycycline, 0.5 μg/ml; ampicillin, 0.25 μg/ml; erythromycin, ≤0.03 μg/ml; vancomycin, 0.5 μg/ml; linezolid, 1 μg/ml; moxifloxacin, 1 μg/ml; ciprofloxacin, >32 μg/ml. Bacterial 16S rRNA gene sequencing was performed by our institution's molecular pathology laboratory with the MicroSeq 500 16S rRNA gene bacterial identification sequencing kit and a 3130 Genetic Analyzer (Applied Biosystems, Foster City, CA) according to the manufacturer's instructions. The sequence data obtained were then compared with known 16S rRNA gene sequences in the GenBank database by BLAST search. Greater than 99.0% identity between the isolate and database sequence was required for identification at both the genus and species levels (with greater than 0.8% separation between different species) (2). Analysis of the isolate's 16S rRNA gene sequence revealed it to be *Lactobacillus delbrueckii* (6).

Based on susceptibility test results and documented allergies, the patient was prescribed a 2-week course of clarithromycin therapy at 250 mg BID, with resolution of her urgency and dysuria and marked improvement of her urinary frequency. Urine studies following the end of therapy showed a significant reduction in the number of urine WBCs (Table 1). A leukocyte esterase test was negative, as was a straight catheter urine culture.

A retroperitoneal ultrasound showed mild cortical thinning of the kidneys secondary to prior reflux, chronic infection, or medical renal disease. There was no evidence of hydronephrosis or stones. There was a partially exophytic, isoechoic mass at the junction of the mid zone and inferior pole of the left kidney measuring approximately 3.4 by 2.6 by 3.7 cm, which partially indented into the renal sinus. Subsequent abdominopelvic magnetic resonance imaging studies revealed multiple peripelvic simple cysts in the bilateral kidneys without solid or enhancing lesions, several areas of cortical thinning in both kidneys, no evidence for hydronephrosis or hydroureter, a nonocclusive clot in the celiac artery, and a small lesion indicating indentation of focal fat into the pancreatic tail. Follow-up

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TABLE 1. Profile of urine studies and cultures[h]

Date	Collection method	No. of WBCs/HPF[f] in urine	No. of squamous cells/LPF[g]	Culture result (CFU/ml)
Current urine studies				
7/02/08[a]	Straight catheter	22	9	Negative
6/24/08[a]	Straight catheter	23	0	Negative
6/9/08	Straight catheter	155	0	>50,000, *Lactobacillus* sp.[e]
5/29/08	Straight catheter	180	0	>50,000, *Lactobacillus* sp.
4/14/08	Straight catheter	ND[b]	ND	>50,000, *Lactobacillus* sp.
Prior urine studies				
2/1/08	Straight catheter	45	10	3,000, *Lactobacillus* sp.
1/7/08	MSCC[c]	180	96	>50,000, *Klebsiella pneumoniae*
11/29/07	Straight catheter	ND	ND	>50,000, *Enterococcus* sp.; >50,000, *Candida albicans*
10/25/07	MSCC	10–25	1–10	Negative
7/31/07	MSCC	10–25	>30	>50,000, *Lactobacillus* sp.
2/28/06	Straight catheter	ND	ND	>50,000, *Lactobacillus* sp.; 100, coagulase-negative *Staphylococcus*
12/6/05	MSCC	0–2	<1	Negative
3/1/05	MSCC	2–5	<1	>50,000, *Lactobacillus* sp.
11/16/04	MSCC	TNTC[d]	10–20	>50,000, *Escherichia coli*
4/20/04	MSCC	ND	ND	Negative
9/13/02	MSCC	25–50	>30	>50,000, *Lactobacillus* sp.

[a] Posttreatment with clarithromycin.
[b] ND, not done.
[c] MSCC, midstream clean catch.
[d] TNTC, too numerous to count.
[e] 16S rRNA gene sequencing revealed this isolate to be *L. delbrueckii*.
[f] HPF, high-power field.
[g] LPF, low-power field.
[h] Unclean samples with numerous mixed organisms not reported.

cystoscopy found an erythematous urethra without lesions, squamous metaplasia of the trigone, efflux of clear urine from both ureteral orifices, the previously documented cystocele, and an area of mild erythema on the right bladder sidewall but no discrete lesions, polyps, stones, or sutures. Urine cytology was negative for any tumor cells.

Lactobacilli are part of the normal bacterial flora of the human vagina, gastrointestinal tract, and oropharynx. They are non-spore-forming, gram-positive bacilli that produce lactic acid from glucose fermentation. Most species of lactobacilli are facultatively anaerobic or microaerophilic and are typically catalase and oxidase negative. Lactobacilli also do not produce H_2S or reduce nitrate to nitrite (8, 11).

Lactobacilli are generally considered to be of low virulence, rarely causing infection in humans. *Lactobacillus* sp. bacteremia has been described primarily in immunocompromised patients following dental manipulations, oral trauma, or endoscopic procedures and as a result of both gastrointestinal tract fistulas and gynecologic neoplasms (1, 11). Subsequent development of endocarditis has been observed in bacteremic patients with preexisting valvular defects (1, 11). Lactobacilli have also been shown to cause neonatal meningitis after vertical transmission of organisms from mother to infant during birth (11).

Urinary tract infections caused by *Lactobacillus* spp. are exceedingly uncommon. Our review of the literature revealed only one previously published case report of a 66-year-old diabetic male who developed acute renal failure and sepsis in a setting of ureteral obstruction. The patient's urine and blood yielded pure cultures of *Lactobacillus gasseri*, and following treatment with amoxicillin, the patient recovered fully (3).

Indeed, in the genitourinary tract, vaginal colonization with lactobacilli provides a natural, nonspecific defense mechanism against infection. Lactic acid production results in a lowering of the regional pH which, when combined with hydrogen peroxide production by commensal anaerobic bacteria, interferes with colonization of the vaginal mucosa by potentially uropathogenic bacteria. Lactobacilli also interfere with the adherence of would-be pathogens by production of biosurfactants such as surlactin and other antiadhesive, surface-active proteins (5, 10, 11). Because of these properties, lactobacilli are employed in probiotic preparations, the use of which is thought by some to represent an effective approach to preventing and even treating urinary tract infections (5, 9). Notwithstanding the relatively common use of *Lactobacillus* spp. in probiotic applications, an increase in secondary infections due to lactobacilli has not been definitively demonstrated (1, 11).

The evidence for *L. delbrueckii* being the cause of urinary tract infection in the patient described herein is convincing. As shown in Table 1, a *Lactobacillus* sp. was recovered repeatedly in significant quantities, usually in pure culture, from both midstream voided and straight catheter urine specimens from our patient over a 6-month period of time during which she remained nearly constantly symptomatic. Significant pyuria also persisted over this time. On three occasions during this interval, she received a course of therapy with ciprofloxacin and the therapy failed. Her isolate of *L. delbrueckii* was found to be high-level resistant to ciprofloxacin. When finally treated

with clarithromycin, an antimicrobial agent to which her isolate was susceptible, she promptly responded to therapy. Follow-up urine cultures were negative, and her pyuria cleared. During the 2 months since the resolution of her symptoms, her infection has not recurred. In addition, numerous urine nitrite tests performed during the period our patient was symptomatic were all negative despite persistent pyuria. *Lactobacillus* does not reduce nitrate. Finally, several urine specimens obtained from our patient while she was symptomatic were found to be markedly acidic (pH = 5.0). *Lactobacillus* is an acid-producing bacterium.

We are confident that the extensive culture work-up of our patient excluded other typical bacterial uropathogens as a cause of her disease. We cannot completely exclude organisms such as *Mycoplasma hominis* or *Ureaplasma urealyticum* as being responsible for her symptoms; however, infection due to either of these organisms would have been expected to respond to ciprofloxacin treatment. As noted above, our patient received three courses of ciprofloxacin therapy with absolutely no resolution of her symptoms.

The pathogenesis of infection in our patient is obscure. One intriguing possibility was that our patient acquired her infecting strain of *L. delbrueckii* through prior use of probiotic preparations; however, she denied any history of probiotic administration. *L. delbrueckii* is commonly used in the preparation of numerous dairy food products, primarily yogurts and cheeses (8, 11). A second possibility is that our patient first developed vaginal colonization with *L. delbrueckii* as a consequence of acquiring this organism from ingested foods. She then went on to develop persistent infection with this relatively avirulent bacterium as a consequence of all of the antecedent pathology present in her genitourinary tract, which could predispose to urinary tract infection.

Recently, Imirzalioglu and colleagues used denaturing high-performance liquid chromatography analysis combined with 16S rRNA gene sequencing to identify the fraction of fastidious and anaerobic bacteria in clinical specimens that may not be recognized by routine laboratory urine culture methods (4, 7). Of the 1,449 urine specimens analyzed in their study, 37 samples were found to be culture negative and PCR positive (all of which were also positive for leukocyte esterase), compared to 128 culture-positive and PCR-positive samples. Numerous fastidious and anaerobic bacteria were identified, several of which are known to cause female genitourinary tract infections. What was of particular interest was the finding that approximately 16% of the culture-negative, PCR-positive urine samples contained *Lactobacillus* species as the sole microorganism whose genetic material could be recovered. Their study identified four different species of lactobacilli, *Lactobacillus crispatus*, *L. gasseri*, *L. iners*, and *L. jensenii*. This finding led the authors to suggest that certain lactobacilli maybe capable of causing urinary tract infections as opportunistic pathogens.

In conclusion, we report a case of a patient with recurrent urinary tract infections in which *L. delbrueckii* was determined to be the etiologic agent. This case illustrates that in select situations, *Lactobacillus* spp. should not be regarded as simply a contaminant but as an unlikely, yet significant, cause of urinary tract inflammation and symptoms in otherwise immunocompetent female patients.

REFERENCES

1. **Cannon, J. P., T. A. Lee, J. T. Bolanos, and L. H. Danziger.** 2005. Pathogenic relevance of *Lactobacillus*: a retrospective review of over 200 cases. Eur. J. Clin. Microbiol. Infect. Dis. **24:**31–40.
2. **Clinical and Laboratory Standards Institute.** 2008. Interpretive criteria for identification of bacteria and fungi by DNA target sequencing; approved guideline MM18-A. Clinical and Laboratory Standards Institute, Wayne, PA.
3. **Dickgiesser, U., N. Weiss, and D. Fritsche.** 1984. Lactobacillus gasseri as the cause of septic urinary infection. Infection **12:**14–16.
4. **Domann, E., G. Hong, C. Imirzalioglu, S. Turschner, J. Kühle, C. Watzel, T. Hain, H. Hossain, and T. Chakraborty.** 2003. Culture-independent identification of pathogenic bacteria and polymicrobial infections in the genitourinary tract of renal transplant recipients. J. Clin. Microbiol. **41:**5500–5510.
5. **Falagas, M. E., G. I. Betsi, T. Tokas, and S. Athanasiou.** 2006. Probiotics for prevention of recurrent urinary tract infections in women: a review of the evidence from microbiological and clinical studies. Drugs **66:**1253–1261.
6. **Germond, J. E., L. Lapierre, M. Delley, B. Mollet, G. E. Felis, and F. Dellaglio.** 2003. Evolution of the bacterial species *Lactobacillus delbrueckii*: a partial genomic study with reflections on prokaryotic species concept. Mol. Biol. Evol. **20:**93–104.
7. **Imirzalioglu, C., T. Hain, T. Chakraborty, and E. Domann.** 2008. Hidden pathogens uncovered: metagenomic analysis of urinary tract infections. Andrologia **40:**66–71.
8. **Murray, P. R., E. J. Baron, J. H. Jorgensen, M. L. Landry, and M. A. Pfaller (ed.).** 2007. Manual of clinical microbiology, 9th edition. ASM Press, Washington, DC.
9. **Senok, A. C., A. Y. Ismaeel, and G. A. Botta.** 2005. Probiotics: facts and myths. Clin. Microbiol. Infect. **11:**958–966.
10. **Velraeds, M. M., B. van de Belt-Gritter, H. C. van der Mei, G. Reid, and H. J. Busscher.** 1998. Interference in initial adhesion of uropathogenic bacteria and yeasts to silicone rubber by a Lactobacillus acidophilus biosurfactant. J. Med. Microbiol. **47:**1081–1085.
11. **Winn, W., Jr., S. Allen, W. Janda, E. Koneman, G. Procop, P. Schreckenberger, and G. Woods.** 2006. Koneman's color atlas and textbook of diagnostic microbiology, 6th edition. Lippincott Williams & Wilkins, Baltimore, MD.